Title	An investigation of the effects of procalcitonin testing on antimicrobial prescribing in respiratory tract infections in an Irish university hospital setting: a feasibility study
Authors	O'Riordan, Frank;Shiely, Frances;Byrne, Stephen;O'Brien, Deirdre;Palmer, B.;Dahly, Darren L.;O'Connor, Terence M.;Curran, David R.;Fleming, Aoife
Publication date	2019-07-19
Original Citation	O'Riordan, F., Shiely, F., Byrne, S., O'Brien, D., Palmer, B., Dahly, D., O'Connor, T. M., Curran, D. and Fleming, A. (2019) 'An investigation of the effects of procalcitonin testing on antimicrobial prescribing in respiratory tract infections in an Irish university hospital setting: a feasibility study', Journal of Antimicrobial Chemotherapy, 74(11), pp. 3352-3361. doi: 10.1093/jac/dkz313
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1093/jac/dkz313
Rights	© The Author(s) 2019. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. All rights reserved. This is a pre-copyedited, author-produced PDF of an article accepted for publication in Journal of Antimicrobial Chemotherapy following peer review. The version of record is available online at: https://academic.oup.com/jac/article/74/11/3352/5536342
Download date	2023-05-05 02:27:53
Item downloaded from	http://hdl.handle.net/10468/9021

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

An investigation of the effects of procalcitonin testing on antimicrobial prescribing in respiratory tract infections in an Irish University Hospital setting - a feasibility study.

F. O'Riordan [1,2]*, F. Shiely[3,4], S. Byrne[2], D. O'Brien[5], B. Palmer[3,4], D. Dahly[3,4], T. O'Connor[6], D. Curran[6], A. Fleming[2,1]

1. Pharmacy Department, Mercy University Hospital, Grenville Place, Cork, Ireland

2. Clinical Pharmacy Research Group, School of Pharmacy, University College Cork, Cork, Ireland.

3. HRB Clinical Research Facility Cork, Mercy University Hospital, Grenville Place, Cork, Ireland

4. School of Public Health, University College Cork, Cork, Ireland

5. Department of Microbiology, Mercy University Hospital, Grenville Place, Cork, Ireland.

6. Department of Respiratory Medicine, Mercy University Hospital, Grenville Place, Cork, Ireland.

Synopsis

Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for antimicrobial prescribing for respiratory tract infections (RTIs). Procalcitonin (PCT) has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with RTIs but recent study results have been variable.

Methods

We conducted a feasibility study of the introduction of PCT testing in patients admitted to hospital with a lower RTI to determine if PCT testing is an effective and worthwhile intervention to introduce to support the existing AMS programme and safely decrease antimicrobial prescribing in patients admitted with RTIs.

Results

A total of 79 patients were randomised to the intervention PCT guided treatment group and 40 patients to the standard care respiratory control group.

The addition of PCT testing led to a significant decrease in duration of antimicrobial prescriptions (mean 6.8 versus 8.9 days p=0.012) and decreased length of hospital stay (median 7 versus 8 days, p=0.009) between the PCT and respiratory control group. PCT did not demonstrate a significant reduction in antimicrobial consumption when measured as DDDs and days of therapy.

Conclusions

PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. The successful implementation of PCT testing in a randomised controlled trial requires an ongoing comprehensive education programme, greater integration into the AMS programme and delivery of PCT results in a timely manner. This feasibility study has shown that a larger randomised controlled trial would be beneficial to further explore the positive aspects of these findings.

Introduction

Antimicrobial resistance (AMR) is a major risk to public health globally that leads to increasing healthcare costs, treatment failure, and increased morbidity and mortality.[1-3] There is a strong association between sub-optimal antimicrobial prescribing and AMR.[4] To optimise prescribing, hospital antimicrobial stewardship (AMS) programmes should target areas of high antimicrobial prescribing. One such area is respiratory tract infections (RTIs). Shorter antimicrobial courses offer one potential solution to the overuse of antimicrobials for RTIs[5] and there is evidence to support such strategies[6 7] even in severe hospital infections.[8]

Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for antimicrobial prescribing for RTIs.[9-12] This contributes to over-use and/or sub-optimal use of antimicrobials[13 14] for RTIs such as community acquired pneumonia (CAP), including prolonged treatment courses of up to 11 days,[15] without a correlation between duration of treatment and infection severity.[15 16] Physicians are often reluctant to shorten antimicrobial course durations due to the fear of incomplete pathogen eradication which could potentially lead to relapse and associated morbidity and mortality.[6] There is also a high rate of antimicrobial continuation where viral infections,[17] including influenza,[18] are identified due to overriding concerns about secondary bacterial infections. However, a recent study has shown a bacterial co-infection rate of only 40%.[11]

To address these issues, there is a growing interest in the use of novel diagnostic techniques and biomarkers as an AMS tool.[19] It is important that AMS programmes investigate the opportunity afforded by these new techniques and the potential they offer to optimise antimicrobial treatment more promptly[20] and change prescribing behaviour.[21] Procalcitonin (PCT) testing is one such diagnostic technique. PCT is a peptide precursor to the hormone calcitonin. It is usually undetected but is upregulated in response to a bacterial infection following stimulation of bacterial-induced cytokines.[22] Upregulation of PCT is blocked in viral infections due to the release of the cytokine interferon gamma, resulting in a higher specificity of PCT to distinguish between bacterial and viral infections when compared to other inflammatory markers such as CRP.[23] PCT levels decrease rapidly when patients

63 are recovering from infection.[24] Hence it offers the potential to support clinical decision making for
64 the initiation and discontinuation of antimicrobials in patients with a clinical suspicion of a bacterial
65 infection when considered along with the clinical assessment of the patients. PCT has been shown to
66 support prescribing decisions and reduce antimicrobial use safely in patients with RTIs[25-28] but findings
67 from recent studies have been variable,[29 30] so it is unclear if it is an effective intervention as part of
68 an AMS programme.
69 The purpose of this study was to conduct a feasibility study to determine if PCT testing is an effective
70 and worthwhile intervention to introduce in a University Teaching Hospital to support the existing
71 AMS programme and safely decrease antimicrobial prescribing in patients admitted with RTIs.
72

73 **Methods**

74 We conducted a single centre, randomised, open-label feasibility study of the introduction of PCT
75 testing in patients admitted to hospital with a lower RTI under the care of the respiratory medicine
76 team during on-call acute unselected general medical take to determine if PCT testing had an impact
77 on antimicrobial consumption and patient's length of stay (LOS) in hospital. The study was conducted
78 in a single 321 bed inner city, voluntary acute University Teaching Hospital, which is part of the
79 South/South West Hospital Group[31] in the Republic of Ireland. It is a Model 3 (smaller general) [32]
80 hospital with a 24-hour emergency department, ICU and admits undifferentiated acute medical and
81 surgical patients. The hospital has an established AMS programme and no significant changes were
82 made to the AMS policies or programme during this study.

83 **Ethics**

84 The study was approved by the local ethics committee (approval code ECM 4 (w) and ECM 3 (III)).
85 Written informed consent was obtained from all participants prior to study enrolment.

86 **Education and training**

The microbiology laboratory scientists received technical advice and training on the operation of the PCT assay from the manufacturer prior to study commencement. They also received a presentation on the introduction of PCT testing in the hospital.

The respiratory medicine team received presentations at the respiratory journal club meetings and provision of written materials electronically. Presentations consisted of evidence supporting PCT use in practice, limitations of PCT testing, PCT measurement, and interpretation using a PCT-based antimicrobial prescribing algorithm (Supplementary material S1). Presentations were given prior to the study commencement and following medical staff rotation changes. The study protocol (Supplementary material S2), study flow chart and the PCT-based antimicrobial prescribing algorithm was provided to all physicians electronically.

Recruitment and consent

Inclusion criteria

Adult patients ≥18 years of age, admitted to hospital under the care of the respiratory teams with an initial diagnosis of an acute lower RTI (i.e. Community acquired pneumonia [33] with severity defined by CURB-65 score[34], Lower RTIs[35], exacerbation of asthma[36], COPD[37], bronchiectasis[38], interstitial lung disease[39] and influenza[35]) and commenced on antimicrobial therapy were identified from the daily admission census or by the respiratory medicine teams.

The randomisation process stratified patients according to presence or absence of severe COPD GOLD Stage D criteria 2017[37] to ensure balanced treatment allocation. Patients were then randomly allocated in a 2:1 ratio to either the PCT guided treatment group or the standard care respiratory control group. Randomisation was carried out using sequentially numbered opaque sealed envelopes. A second general control group of patients admitted under general medicine teams with a diagnosed acute lower RTI and received standard care (no PCT measurement) was recruited to provide a comparison of antimicrobial prescribing in RTIs by non-respiratory specialist physicians in the hospital.

Exclusion Criteria

Exclusion criteria were: unable to give written informed consent due to language restrictions, cognitive impairment or severe dementia; re-admission to hospital within 30 days of previous admission; immunosuppression (neutropenic, chemotherapy, radiation therapy or immunosuppressive therapy) other than corticosteroid use; life-threatening medical co-morbidities leading to possible imminent death, Do Not Resuscitate (DNR) status; patients with concurrent chronic infections necessitating prolonged antimicrobial treatment (cystic fibrosis, tuberculosis, infective endocarditis, osteo-articular infections, hepatic or cerebral abscesses, chronic prostatitis); patients with >24 hours of appropriate antimicrobial therapy prior to initial PCT level; active intravenous drug users; pregnant women.

Intervention

PCT testing was commenced in the microbiology department following completion of staff training and instrument validation. It was available during routine working hours (Monday to Friday, 9am-5pm). PCT serum concentrations were measured using the VIDAS BRAHMS PCT (assay range 0.05-200 µg/L) (Biomerieux, France).

PCT serum concentrations were interpreted using an evidence based algorithm (Supplementary material S1)[40] which has been validated in previous studies[28 29] recommending antimicrobials strongly discouraged for PCT levels < 0.1 µg per litre, discouraged for levels 0.1 to 0.25 µg/L, encouraged for levels > 0.25 to 0.5 µg/L and strongly encouraged for levels > 0.5 µg/L. The algorithm also included specific overruling criteria where antimicrobials could be considered in the case of respiratory or haemodynamic instability; life-threatening co-morbidity; need for ICU admission; PCT < 0.1 µg /mL: CAP with CURB 65 > 3, COPD stage IV; PCT < 0.25 µg/mL: CAP with CURB 65 > 2; localised infection (abscess, empyema); immunocompromised (other than corticosteroids); concomitant infection in need of antimicrobials.

The antimicrobial prescribing advice generated from the PCT algorithm was verbally communicated to the respiratory medicine team and this advice was non-binding. The respiratory medicine team retained prescribing autonomy regarding clinical decisions irrespective of the PCT level or algorithm generated antimicrobial prescribing advice. The algorithm adherence for antimicrobial prescribing recommendations was recorded at 24 hours following the PCT test for all patients along with the rational for prescribing decisions. Algorithm adherence was defined as antimicrobial therapy that was continued or discontinued in accordance with the PCT cut-off ranges. Non-adherence was defined as antimicrobial therapy that was not discontinued despite low PCT levels. Over-riding criteria were not considered when measuring adherence but were recorded as reasons for non-adherence.

Patients were followed until their discharge. A further follow up of medical records took place at 30 days post admission to identify re-admitted patients and re-admitted patients with infection re-lapse.

Patient recruitment ran from June 1st 2017 to May 31st 2018. Figure 1 represents the patient hospital journey with a respiratory tract infection.

Outcomes

The primary outcomes were to quantify the individual inpatient antimicrobial consumption, prescription duration and the inpatient LOS. Following a recent systematic review which recommended that antimicrobial use should be expressed in at least two metrics simultaneously, [41] antimicrobial consumption was measured using DDDs, days of therapy (DOTs) and prescription duration. DDDs were calculated using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) index of the WHO Collaborating Centre for Drug Statistics Methodology [42] but were not adjusted for hospital activity. Days Of Therapy (DOT)[43] calculates individual patient-days of antimicrobial exposure and accounts for dosing and frequency of each drug. Antimicrobial prescription duration was measured in days (defined as the number of days between the commencement and discontinuation of antimicrobials). The LOS was defined as date of discharge less date of admission.

Secondary outcomes were number of infection and antimicrobial related adverse events during in-patient LOS including mortality, hospital re-admission, and infection re-lapse requiring re-admission both within 30 days. Algorithm adherence for antimicrobial prescribing recommendations was measured.

A qualitative process evaluation of the study was conducted in parallel with this feasibility study and will be reported in a subsequent paper.

Statistical methods

A Microsoft Access database (version 1903) was developed to record the study data. Statistical analysis was conducted using R (version 3.4.0) and was conducted on an intention to treat basis.

The primary outcome of antimicrobial consumption between the PCT and respiratory control arms was evaluated using the non-parametric Wilcoxon Rank Sum test. A Kaplan-Meier curve was used to analyse the median time to discharge between the PCT and respiratory control group.

Chi-square tests were used to evaluate differences between the PCT and respiratory control arms for all secondary outcomes - number of adverse events, re-admission and infection re-lapse requiring re-admission both within 30 days.

Results

The respiratory medical teams admitted 823 general medical patients of whom 313 patients were classified as a respiratory infection or respiratory disorder during the recruitment period of June 1st 2017 to May 31st 2018. A CONSORT flow diagram of recruitment can be seen in figure 2.

A further 48 patients were recruited to the general control group. Three patients who were identified as suitable to enter the general control group were not recruited due to confusion, isolation due to infection and refused consent.

Demographic data and study overview are contained in Table 1. Clinical findings of patients on admission to hospital are contained in Table 2.

There were several differences between the baseline characteristics of the PCT group and respiratory control group. The PCT group contained more male patients (60% versus 42%), active smokers (25% versus 12.5%) and patients with pre-existing COPD A-C (29% versus 17%).

There were a number of differences in final diagnosis between the PCT group and the respiratory control group with asthma (3.8% versus 15%), CAP (10% versus 7.5%), LRTI (30.4% versus 17.5%. CAP severity in the PCT group had CURB-65 scores ranging from 0 to 3 with a mean of 1.87 while the CAP severity in the respiratory control group had CURB-65 scores ranging from 0 to 1 with a mean of 0.66.

The clinical findings on admission were similar between group with two exceptions where the PCT group had a higher percentage of patients who were productive of sputum on admission (49% versus 37%) and patients prescribed antibiotics prior to admission (35% versus 25%).

Procalcitonin testing and results

The 79 patients randomised to the PCT group had a total of 163 PCT levels taken (median of 2 tests per patient (range 1-6). Overall the PCT levels had a median of 0.075µg/L (IQR 0.05 – 0.26). The initial PCT level was ≤0.24 µg/L for 58 patients (including 38 patients with an initial PCT level of ≤0.05 µg/L). Our primary outcome was to determine the inpatient antimicrobial consumption, duration of antimicrobial treatment and hospital LOS. The main outcomes can be seen in Table 3 and Figure 3. Statistical analysis was conducted on the PCT and respiratory control groups and does not include comparison with the general control group.

There was no significant difference in antimicrobial exposure or usage per patient when measured as DDD (11.1 ± 7.5 versus 13.1 ± 10.7, p=0.218) (mean $\pm$ SD) or DOT (8.9 ± 6.3 versus 11 ± 7.6, p=0.077) of patients between the PCT and respiratory control group. Median values of both metrics DDD (8.66 versus 9.57) and DOT (7.5 versus 8.25) showed a decrease of 9% in antimicrobial consumption per patient.

There was a significant difference in the antimicrobial duration in days between the PCT and respiratory control groups (median 7 versus 8 days, p=0.0125). There was also a significant difference between the PCT and respiratory control groups in the median LOS (p=0.009) and this can also be seen in the Kaplan–Meier curves in Figure 4.

In the analysis of secondary outcomes there was no significant differences between the PCT and respiratory control groups in the incidence of adverse events during in-patient hospital stay (p=0.9852), the rate of hospital re-admission (p=0.1507), and the rate of infection re-lapse requiring re-admission both within 30 days (p=0.0924).

Algorithm compliance is displayed in table 4.

Overall PCT algorithm compliance per patient was 35% within 24 hours of PCT level being taken. 25 patients had high PCT levels ($\geq$ 0.25 µg/L) where the algorithm recommendation was to continue

antimicrobial treatment and algorithm compliance was 100%. 67 patients had low PCT levels (< 0.25 μg/L) where the algorithm recommendation was to discontinue antimicrobial treatment and algorithm compliance was low (10%). In these instances, the reasons for non-adherence were based on a clinical decision in 55/112 (49%) PCT levels with the remaining 57/112 (51%) PCT levels based on meeting various algorithm overriding criteria (respiratory or haemodynamic instability; life threatening co-morbidity; need for ICU admission; localised infection (abscess, empyema)).

Seven patients had their antimicrobial treatment discontinued in compliance with the algorithm when PCT levels were low (< 0.25 μg/L). This resulted in shorter course lengths in five patients (< 7 days) 1 course length completion as planned at 7 days, and early antimicrobial discontinuation (day 2) in a patient with influenzae. There were no hospital readmissions among these patients.

In a further 9 patients where there was initial non-compliance with the algorithm recommendations when measured at 24 hours, their antimicrobial treatment was subsequently modified resulting in a shorter course length in 7 patients (< 7 days) and 2 further patients discontinued antimicrobials prior to discharge (1 patient re-admitted with infection).

Algorithm compliance by indication was as follows; CAP (80%), asthma (50%) LRTI (30%), COPD (12.5%) and influenza virus (42%). PCT levels and algorithm compliance were found to be low in patients with COPD stage D and structural lung conditions like bronchiectasis and interstitial lung disease. In these cases, the clinical judgement of physicians was to over-ride the algorithm recommendations and continue antimicrobials.

Microbiology positive specimens

38 patients (23%) had positive microbiology results : 13 influenzae virus, 10 bacterial isolates from respiratory specimens and 7 yeast isolates from respiratory specimens.

Adverse events

Infection and antimicrobial related adverse events included gastro-intestinal (antimicrobial related diarrhoea 1 patient) renal function (acute kidney injury secondary to antimicrobials 1 patient), liver function (increased liver function tests secondary to antimicrobials 1 patient), respiratory disorders (hospital acquired pneumonia, hospital acquired influenzae, respiratory deterioration, 3 patients) and other events 2 patients.

Mortality during the study

Five patients included in the study died during their hospital stay, four from the PCT group and one from the respiratory control group (age range 75-94 years). All had multiple co-morbidities including cardiac (congestive cardiac failure, atrial fibrillation), renal and new or existing cancer diagnosis. Antimicrobial treatment decisions for these patients were based on clinical decisions.

Discussion

This feasibility study of the introduction of PCT testing has shown a positive effect on antimicrobial prescribing resulting in a decrease in the duration of antimicrobial courses in patients with RTIs and a decrease in LOS without an increase in adverse events or re-admission to hospital. The median duration of antimicrobial treatment was reduced from 8 to 7 days and antimicrobial consumption fell by 9% when measured as DDD and DOT. This study confirms the findings of previous PCT trials[28 44] that it is an effective and worthwhile intervention to safely reduce antimicrobial exposure in patients with RTIs and supporting the AMS programme. However, there were several findings which may have influenced the outcomes and these need to be considered when viewing the overall results and considering progression to and design of a full randomised controlled trial (RCT).

Overall PCT algorithm compliance was 35%, and compliance with stopping recommendations was 10% when PCT levels were low (<0.25 μg/L). The reasons for non-compliance were clinical judgement (49%) and meeting pre-determined over-riding criteria (51%). PCT was a new diagnostic test in the hospital and physicians can require time to become familiar with and develop confidence in the use of PCT testing.[45] Other studies have found algorithm compliance can be variable ranging from 35% to 80%.[44] An international, multicentre study found that centres with experience of using PCT and ongoing reinforcement of PCT guided AMS had higher algorithm compliance than PCT naive centres.[44] Protocol driven studies[28 46] have also shown higher algorithm compliance and greater impact on antimicrobial prescriptions than studies taking a quality improvement implementation approach.[29]

Algorithm compliance must improve significantly in a future trial to maximise the potential impact of PCT testing on antimicrobial prescribing decisions but also acknowledging the limitations of PCT and that physicians cannot rely on PCT alone to guide antibiotic therapy.[23] In a future trial this should be addressed by a more comprehensive educational programme and more effective incorporation into the AMS programme to re-enforce PCT recommendations. Such an approach has been shown to be effective[30 46 47] and required for interventions such as PCT to realise their full benefit.[19] The educational

element of this study may not have been sufficient. A future trial should consider the inclusion of more frequent educational presentations prior to and during the intervention and include case reviews of PCT patients. Consideration should be given to the development of pocket cards, incorporation into local electronic antimicrobial prescribing guidelines and availability of results on the hospital electronic laboratory system.[46]

Delays in availability of PCT results may have also decreased the impact of the intervention and contributed to poor algorithm compliance with 38% of PCT serum results not available until the next day (24 hours after the serum sample was taken). This included results which were delayed or unavailable for 12 patients until after they were discharged. In a future trial prompt availability of PCT levels is important. This would allow physicians to consider PCT along with routine biochemistry and blood analysis, and the patients' clinical parameters at the point of care when making antimicrobial prescribing decisions. Consideration should be given to measurement of algorithm adherence at 48 hours to account for unforeseen delays PCT result availability or delayed physician review of PCT results.

There were several factors involved in patient recruitment which may have influenced the primary outcomes of the study and should be addressed in a future trial design. These were the variation in infection severity between the PCT and respiratory control groups and the inclusion of patients who were already prescribed antimicrobials prior to hospital admission. These factors can be addressed in a suitably powered future RCT with the inclusion of illness severity scores, along with the use of multivariate and sub-group analysis.

A future RCT would include a broader range of physicians rather than respiratory specialists alone. Antimicrobial consumption in the general control group of patients in this study was higher than in either of the respiratory groups. The addition of a PCT testing to the existing AMS programme may have the potential to have a greater impact on this patient group.

Strengths and limitations

The study was conducted in a setting where PCT was a newly available test to physicians. A broad range of RTIs were recruited and the study took place over a calendar year and included seasonal variation in illness and prescribing. Patients were randomised to intervention or control, thus reducing selection bias. Serial PCT measurements were available to guide antimicrobial prescribing.

The study had some limitations. The study population had a clinical need for antimicrobial treatment so the study was designed to examine the duration of therapy and LOS, rather than investigating the potential to withhold antimicrobial therapy. The study results may have been influence by a study effect. Both the PCT and respiratory control groups were treated by the same group of physicians who all received education and as they were aware that their behaviour was being monitored which may have resulted in a Hawthorn effect.[48] The intervention was limited to one medical speciality which may limit its generalisability to other medical specialties and settings. The need for consent and PCT results which were not available at the point of clinical decision making in a small number of cases.

Conclusion

PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. Several factors were identified which may have influenced the outcomes and the intervention implementation. The successful implementation of PCT testing requires an ongoing comprehensive education programme, greater integration into the AMS programme and delivery of PCT results in a timely manner. This feasibility study has shown that a larger randomised controlled trial would be beneficial to further explore the positive aspects of these findings.

Acknowledgements

The authors would like to thank the Medical teams and the Microbiology department for their involvement in the study. We would like to thank Professor Joe Eustace HRB Clinical Research Facility Cork for his advisory input into the study. We would like to thank BioMeriux for placement of the miniVIDAS instrument for the duration of the study and staff training.

Funding

This work was funded by an educational grant from the Cork & Kerry Regional Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) committee.

Transparency declarations

Nothing to declare.

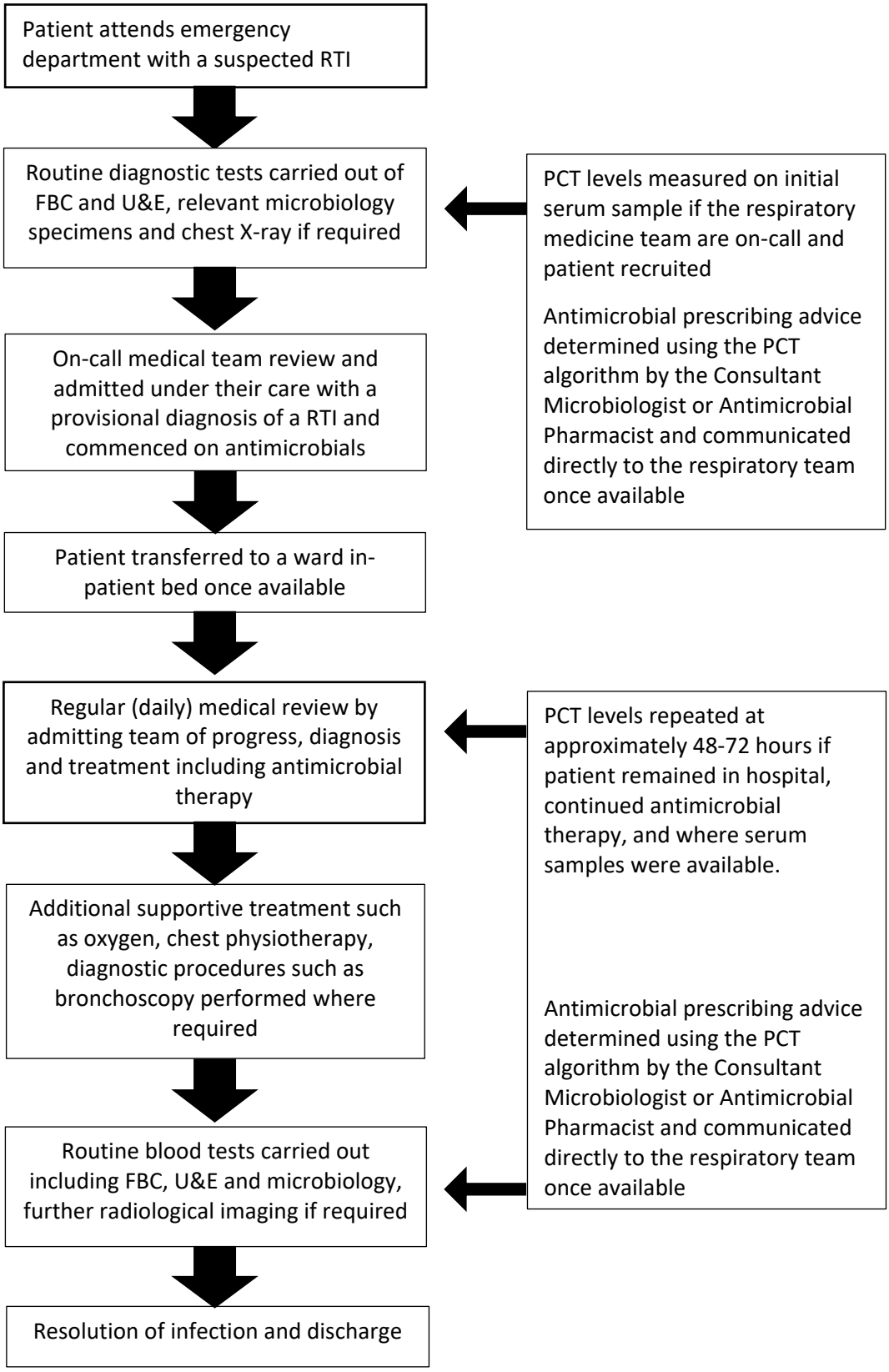
References

1. Organisation WH. Antimicrobial resistance: global report on surveillance 2014. *Accessed from* *http://appswhoint/iris/bitstream/handle/10665/112642/9789241564748_engpdf;jsessionid=ADE8F88FCAD18345935219F29F7868E0?sequence=1* 2014
2. Tzouvelekis LS, Markogiannakis A, Piperaki E, et al. Treating infections caused by carbapenemase-producing Enterobacteriaceae. *Clin Microbiol Infect* 2014;20(9):862-72. doi: 10.1111/1469-0691.12697 [published Online First: 2014/06/04]
3. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* 2006;42 Suppl 2:S82-9. doi: 10.1086/499406 [published Online First: 2005/12/16]
4. Martin SJ, Micek ST, Wood GC. Antimicrobial resistance: Consideration as an adverse drug event. *Critical Care Medicine* 2010;38
5. Llewelyn MJ, Fitzpatrick JM, Darwin E, et al. The antibiotic course has had its day. *BMJ* 2017;358:j3418. doi: 10.1136/bmj.j3418
6. File TM, Jr. Duration and cessation of antimicrobial treatment. *J Hosp Med* 2012;7 Suppl 1:S22-33. doi: 10.1002/jhm.988 [published Online First: 2012/01/01]
7. El Moussaoui R, Roede BM, Speelman P, et al. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. *Thorax* 2008;63(5):415. doi: 10.1136/thx.2007.090613
8. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *Jama* 2003;290(19):2588-98. doi: 10.1001/jama.290.19.2588 [published Online First: 2003/11/20]
9. Bartlett JG. Diagnostic Tests for Agents of Community-Acquired Pneumonia. *Clinical Infectious Diseases* 2011;52(suppl_4):S296-S304. doi: 10.1093/cid/cir045
10. Carugati M, Aliberti S, Reyes LF, et al. Microbiological testing of adults hospitalised with community-acquired pneumonia: an international study. *ERJ open research* 2018;4(4) doi: 10.1183/23120541.00096-2018 [published Online First: 2018/11/27]
11. Falsey AR, Becker KL, Swinburne AJ, et al. Bacterial complications of respiratory tract viral illness: a comprehensive evaluation. *The Journal of infectious diseases* 2013;208(3):432-41. doi: 10.1093/infdis/jit190 [published Online First: 2013/05/09]
12. Clark T, Medina M-j, Batham S, et al. Adults hospitalised with acute respiratory illness rarely have detectable bacteria in the absence of COPD or pneumonia; viral infection predominates in a large prospective UK sample2014.
13. Blasi F, Garau J, Medina J, et al. Current management of patients hospitalized with community-acquired pneumonia across Europe: outcomes from REACH. *Respiratory Research* 2013;14(1):44. doi: 10.1186/1465-9921-14-44
14. Jenkins TC, Stella SA, Cervantes L, et al. Targets for antibiotic and healthcare resource stewardship in inpatient community-acquired pneumonia: a comparison of management practices with National Guideline Recommendations. *Infection* 2013;41(1):135-44. doi: 10.1007/s15010-012-0362-2 [published Online First: 2012/11/20]
15. Aliberti S, Blasi F, Zanaboni AM, et al. Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia. *The European respiratory journal* 2010;36(1):128-34. doi: 10.1183/09031936.00130909 [published Online First: 2009/11/21]
16. Walsh TL, DiSilvio BE, Speredelozzi D, et al. Evaluation of Management of Uncomplicated Community-Acquired Pneumonia:A Retrospective Assessment. *Infectious Diseases in Clinical Practice* 2017;25(2):71–75. doi: 10.1097/ipc.0000000000000468
17. Shiley KT, Lautenbach E, Lee I. The Use of Antimicrobial Agents after Diagnosis of Viral Respiratory Tract Infections in Hospitalized Adults: Antibiotics or Anxiolytics? *Infection Control & Hospital Epidemiology* 2010;31(11):1177-83. doi: 10.1086/656596 [published Online First: 2015/01/02]

18. Lee JJ, Verbakel JY, Goyder CR, et al. The clinical utility of point-of-care tests for influenza in ambulatory care: A systematic review and meta-analysis. *Clin Infect Dis* 2018 doi: 10.1093/cid/ciy837 [published Online First: 2018/10/05]
19. Anderson DJ, Jenkins TC, Evans SR, et al. The Role of Stewardship in Addressing Antibacterial Resistance: Stewardship and Infection Control Committee of the Antibacterial Resistance Leadership Group. *Clinical Infectious Diseases* 2017;64(suppl_1):S36-S40. doi: 10.1093/cid/ciw830
20. Livermore DM. Of stewardship, motherhood and apple pie. *Int J Antimicrob Agents* 2014;43(4):319-22. doi: 10.1016/j.ijantimicag.2014.01.011 [published Online First: 2014/03/19]
21. O'Neill TRoARCbJ. Rapid diagnostics: Stopping unnecessary use of antibiotics. . *London (UK) HM Government: 2015 Accessed from http:// http://amr-revieworg/sites/default/files/Rapid%20Diagnostics%20-%20Stopping%20Unnecessary%20use%20of%20Antibioticspdf* 2015
22. Linscheid P, Seboek D, Schaer DJ, et al. Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes*. *Critical Care Medicine* 2004;32(8)
23. Self WH, Balk RA, Grijalva CG, et al. Procalcitonin as a Marker of Etiology in Adults Hospitalized With Community-Acquired Pneumonia. *Clin Infect Dis* 2017;65(2):183-90. doi: 10.1093/cid/cix317 [published Online First: 2017/04/14]
24. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. *Crit Care Med* 2008;36(3):941-52. doi: 10.1097/CCM.0B013E318165BABB [published Online First: 2008/04/24]
25. Vollenweider DJ, Jarrett H, Steurer-Stey CA, et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;12:Cd010257. doi: 10.1002/14651858.Cd010257 [published Online First: 2012/12/14]
26. Wedzicha JAEC-C, Miravitlles M, Hurst JR, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *The European respiratory journal* 2017;49(3) doi: 10.1183/13993003.00791-2016 [published Online First: 2017/03/17]
27. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2017;10(10):CD007498. doi: 10.1002/14651858.CD007498.pub3 [published Online First: 2017/10/13]
28. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: The prohosp randomized controlled trial. *Jama* 2009;302(10):1059-66. doi: 10.1001/jama.2009.1297
29. Huang DT, Yealy DM, Filbin MR, et al. Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. *New England Journal of Medicine* 2018;379(3):236-49. doi: 10.1056/NEJMoa1802670
30. Townsend J, Adams V, Galiatsatos P, et al. Procalcitonin-Guided Antibiotic Therapy Reduces Antibiotic Use for Lower Respiratory Tract Infections in a United States Medical Center: Results of a Clinical Trial. *Open Forum Infect Dis* 2018;5(12):ofy327. doi: 10.1093/ofid/ofy327 [published Online First: 2019/01/09]
31. Trusts PtfTEoHGaattIH. The Establishment of Hospital Groups as a transition to Independent Hospital Trusts, A report to the Minister for Health. *Accessed from https://healthgovie/wp-content/uploads/2014/03/IndHospTrustspdf* 2013
32. group Ampw. Report of the National Acute Medicine Programme. *Accessed from https://wwwhseie/eng/services/publications/clinical-strategy-and-programmes/report-of-the-national-acute-medicine-programmepdf* 2010
33. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009;64(Suppl 3):iii1.

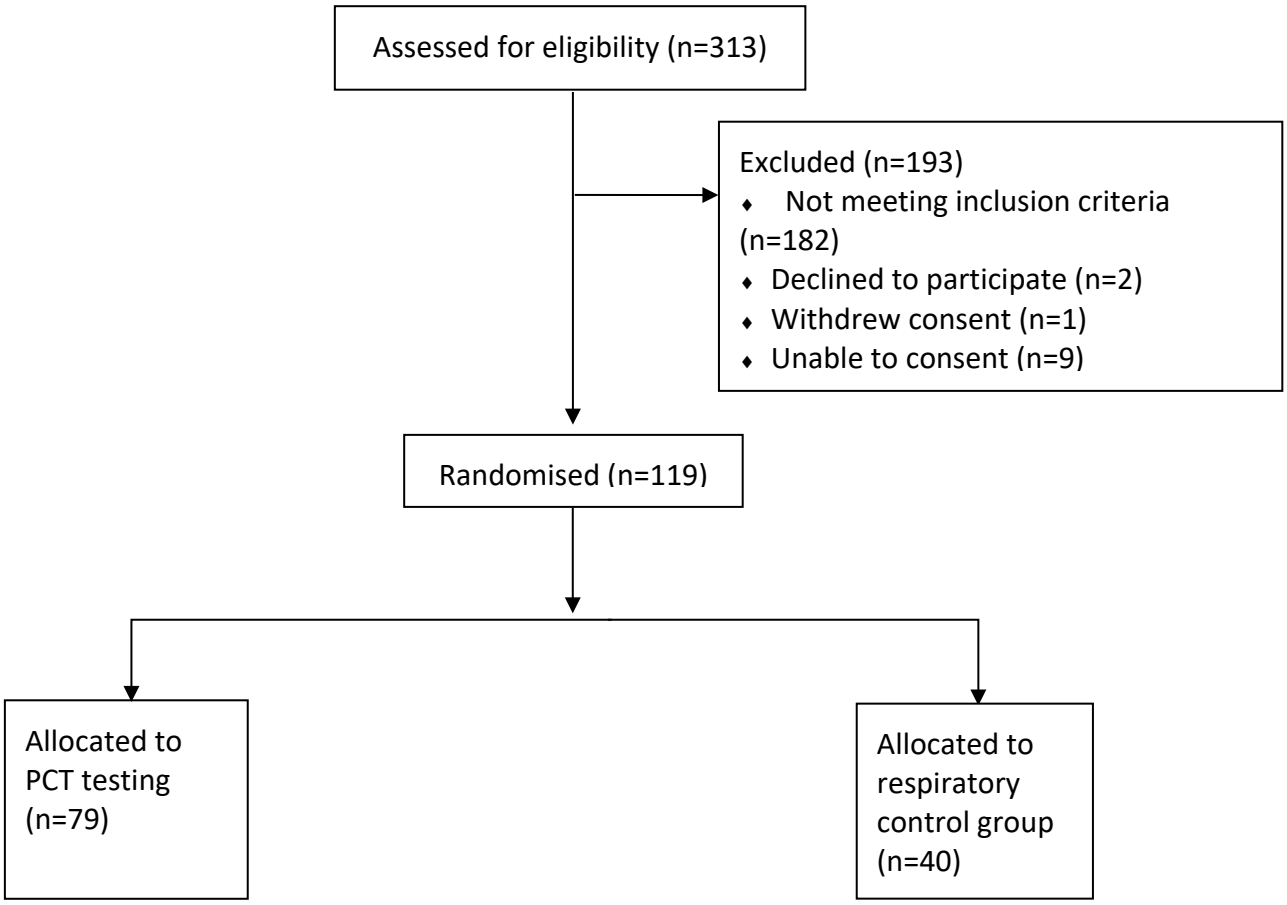
34. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58(5):377-82. [published Online First: 2003/05/03]
35. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections--full version. *Clin Microbiol Infect* 2011;17 Suppl 6:E1-59. doi: 10.1111/j.1469-0691.2011.03672.x [published Online First: 2011/11/02]
36. BTS SBTS, Network SIG. British guideline on the management of asthma. *Thorax* 2014;69(Suppl 1):i1.
37. Global Strategy for the Diagnosis MaPoC, Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD. *Available from: https://goldcopdorg* 2017
38. Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;65(7):577. doi: 10.1136/thx.2010.142778
39. Wells AU, Hirani N. Interstitial lung disease guideline. *Thorax* 2008;63(Suppl 5):v1. doi: 10.1136/thx.2008.101691
40. Schuetz P, Chiappa V, Briel M, et al. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. *Archives of internal medicine* 2011;171(15):1322-31. doi: 10.1001/archinternmed.2011.318 [published Online First: 2011/08/10]
41. Stanic Benic M, Milanic R, Monnier AA, et al. Metrics for quantifying antibiotic use in the hospital setting: results from a systematic review and international multidisciplinary consensus procedure. *J Antimicrob Chemother* 2018;73(suppl_6):vi50-vi58. doi: 10.1093/jac/dky118 [published Online First: 2018/06/08]
42. (WHO) WHO. Collaborating centre for drug statistics methodology. ATC/DDD index 2018. *Available at https://wwwwhoccno/atc_ddd_index/* 2018
43. Polk RE, Fox C, Mahoney A, et al. Measurement of adult antibacterial drug use in 130 US hospitals: comparison of defined daily dose and days of therapy. *Clin Infect Dis* 2007;44(5):664-70. doi: 10.1086/511640 [published Online First: 2007/02/06]
44. Albrich WC, Dusemund F, Bucher B, et al. Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in "real life": an international, multicenter poststudy survey (ProREAL). *Archives of internal medicine* 2012;172(9):715-22. doi: 10.1001/archinternmed.2012.770 [published Online First: 2012/07/12]
45. Gilbert D. Serum procalcitonin levels: Comment on "effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in 'real life'". *Archives of internal medicine* 2012;172(9):722-23. doi: 10.1001/archinternmed.2012.1327
46. Broyles MR. Impact of Procalcitonin (PCT)-Guided Antibiotic Management on Antibiotic Exposure and Outcomes: Real World Evidence. *Open Forum Infectious Diseases* 2017:ofx213-ofx13. doi: 10.1093/ofid/ofx213
47. Walsh TL, DiSilvio BE, Hammer C, et al. Impact of Procalcitonin Guidance with an Educational Program on Management of Adults Hospitalized with Pneumonia. *Am J Med* 2018;131(2):201 e1-01 e8. doi: 10.1016/j.amjmed.2017.08.039 [published Online First: 2017/09/28]
48. Claus CK. B. F. Skinner and T. N. Whitehead: a brief encounter, research similarities, hawthorne revisited, what next? *The Behavior analyst* 2007;30(1):79-86. [published Online First: 2007/04/01]

Figure 1 Patient hospital journey with a respiratory tract infection



RTI: Respiratory tract infection, PCT: procalcitonin, FBC: full blood count, U&E: urea and electrolytes

Figure 2. CONSORT 2010 Flow Diagram



528 **Table 1. Demographic data and study overview**

Variable		Study Group			
		Overall	PCT arm	Respiratory Control arm	General Control arm
Participants		167 (100%)	79 (47.3%)	40 (24.0%)	48 (28.7%)
Gender	Female	79 (47.3%)	31 (39.2%)	23 (57.5%)	25 (52.1%)
	Male	88 (52.7%)	48 (60.8%)	17 (42.5%)	23 (47.9%)
Age (years)		68.7 ± 14	68.6 ± 13.6	68.4 ± 15.3	69.1 ± 13.9
Co-existing conditions and risk factors					
Smoking Status	Non-smoker	50 (30.3%)	26 (32.9%)	13 (32.5%)	11 (23.9%)
	Smoker	33 (20%)	20 (25.3%)	5 (12.5%)	8 (17.4%)
	Ex-smoker	82 (49.7%)	33 (41.8%)	22 (55%)	27 (58.7%)
Asthma		28 (16.8%)	13 (16.5%)	10 (25%)	5 (10.4%)
COPD A-C		58 (34.7%)	23 (29.1%)	10 (25%)	25 (52%)
COPD D		24 (14.4%)	10 (12.7%)	5 (12.5%)	9 (18.8%)
Bronchiectasis		16 (9.6%)	9 (11.4%)	3 (7.5%)	4 (8.3%)
Interstitial lung disease		7 (4.2%)	4 (5%)	2 (5%)	1 (2.1%)
Final diagnosis					
Asthma		11 (6.6%)	3 (3.8%)	6 (15%)	2 (4.2%)
Community acquired pneumonia		18 (10.8%)	8 (10%)	3 (7.5%)	7 (14.6%)
COPD		62 (37.1%)	24 (30.4%)	13 (32.5%)	25 (52%)
Lower respiratory tract infection		45 (27%)	28 (35.4%)	7 (17.5%)	10 (20.8%)
Other lower respiratory tract infections		20 (12%)	10 (12.6%)	7 (17.5%)	3 (6.2%)
Non-respiratory related		11 (6.6%)	6 (7.6%)	4 (10%)	1 (2.1%)

529

530

Table 2. Clinical findings on admission to hospital*

	Total (n = 167)	PCT (n = 79)	Respiratory Control (n = 40)	General control (n = 48)
Respiratory rate- breaths/minute	22.1 ± 5	22.1 ± 5.4	21.1 ± 3.7	22.7 ± 5.2
Systolic blood pressure- mmHg	133 ± 23.1	130.9 ± 22.9	136 ± 20.9	134 ± 25
Diastolic blood pressure- mmHg	75 ± 14.1	74.8 ± 12	78.6 ± 14.8	72.3 ± 16.1
Heart rate- beats/minute	91.8 ± 20.1	93.4 ± 23.3	91.2 ± 16.7	89.8 ± 16.7
Temperature- °C	36.8 ± 0.8	36.8 ± 0.8	36.9 ± 0.8	36.8 ± 0.9
Rigors - no. (%)	24 (14.4%)	11 (13.9%)	6 (15%)	7 (14.6%)
Fever - no. (%)	18 (10.8%)	8 (10.1%)	5 (12.5%)	5 (10.4%)
Chills - no. (%)	15 (9%)	10 (12.7%)	1 (2.5%)	4 (8.3%)
Number of clinical signs of infection	1.8 ± 1.3	1.9 ± 1.3	1.7 ± 1.2	1.8 ± 1.3
Documented signs of respiratory illness				
Cough - no. (%)	132 (79%)	64 (81%)	31 (77.5%)	37 (77%)
Shortness of breath - no. (%)	101 (60.5%)	45 (57%)	23 (57.5%)	33 (68.7%)
Productive of sputum - no. (%)	81 (48.5%)	39 (49.4%)	15 (37.5%)	27 (56.2%)
Dyspnoea - no. (%)	49 (29.3%)	22 (27.8%)	10 (25%)	17 (35.4%)
Pleuritic pain - no. (%)	26 (15.6%)	10 (12.7%)	9 (22.5%)	7 (14.6%)
Respiratory failure - no. (%)	19 (11.4%)	8 (10.1%)	5 (12.5%)	6 (12.5%)
Abnormal chest exam - no. (%)	144 (86.2%)	70 (88.6%)	31 (77.5%)	43 (89.6%)
Abnormal radiological findings - no. (%)	94 (56.3%)	42 (53.2%)	21 (52.5%)	28 (58.3%)
CURB-65 score (CAP patients)	1.56 ± 1.05	1.87 ± 1.05	0.66 ± 0.47	1.57 ± 1.05
Number of signs of acute respiratory illness	3.9 ± 1.4	3.8 ± 1.4	3.8 ± 1.4	4 ± 1.3
Antimicrobials prescribed pre-admission - no. (%)	59 (35.3%)	28 (35.4%)	10 (25%)	21 (43.7%)
Corticosteroids prescribed pre-admission - no. (%)	34 (20.4%)	14 (17.7%)	7 (17.5%)	13 (27%)
Infection source				
Community - no. (%)	149 (89.2%)	70 (88.6%)	32 (80%)	47 (98%)
Healthcare - no. (%)	13 (7.8%)	6 (7.6%)	6 (15%)	1 (2%)
Hospital - no. (%)	5 (3%)	3 (3.8%)	2 (5%)	0 (0%)

*plus minus values are means + SD

Table 3. Primary and secondary outcome data

Primary outcomes Mean ± SD (Median)	PCT (n = 79)	Respiratory Control (n = 40)	General control (n = 48)	p value
Defined daily doses per patient	11.1 ± 7.5 (8.66)	13.1 ± 10.7 (9.57)	18.5 ± 11 (16.5)	0.218
Days of therapy per patient	8.9 ± 6.3 (7.5)	11 ± 7.6 (8.25)	13.7 ± 11.1 (11.63)	0.077
Total duration of inpatient antimicrobials (days)	6.8 ± 2.8 (7)	8.9 ± 4 (8)	8.4 ± 3.6 (8)	0.0125*
Length of hospital stay (days)	7.4 ± 4.3 (7)	10.5 ± 6.1 (8)	8.9 ± 3.8 (8)	0.009*
Secondary outcomes				
Hospital readmission within 30 days	7 (8.9%)	8 (20%)	7 (14.6%)	0.1507
Relapse of infection within 30 days	6 (7.6%)	8 (20%)	6 (12.5%)	0.0924
Adverse events	6 (7.6%)	3 (7.5%)	4 (8.3%)	0.9852

**= statistical significance was set as <0.05, p-values relate to the comparison between the PCT and respiratory control groups*

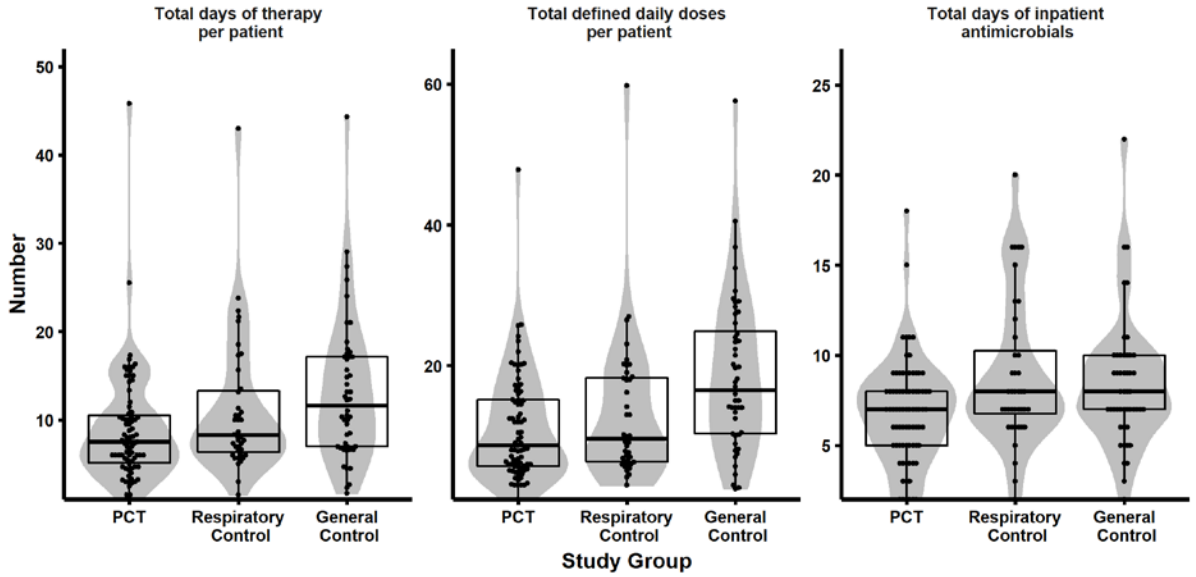


Figure 3. Main antimicrobial consumption outcomes.

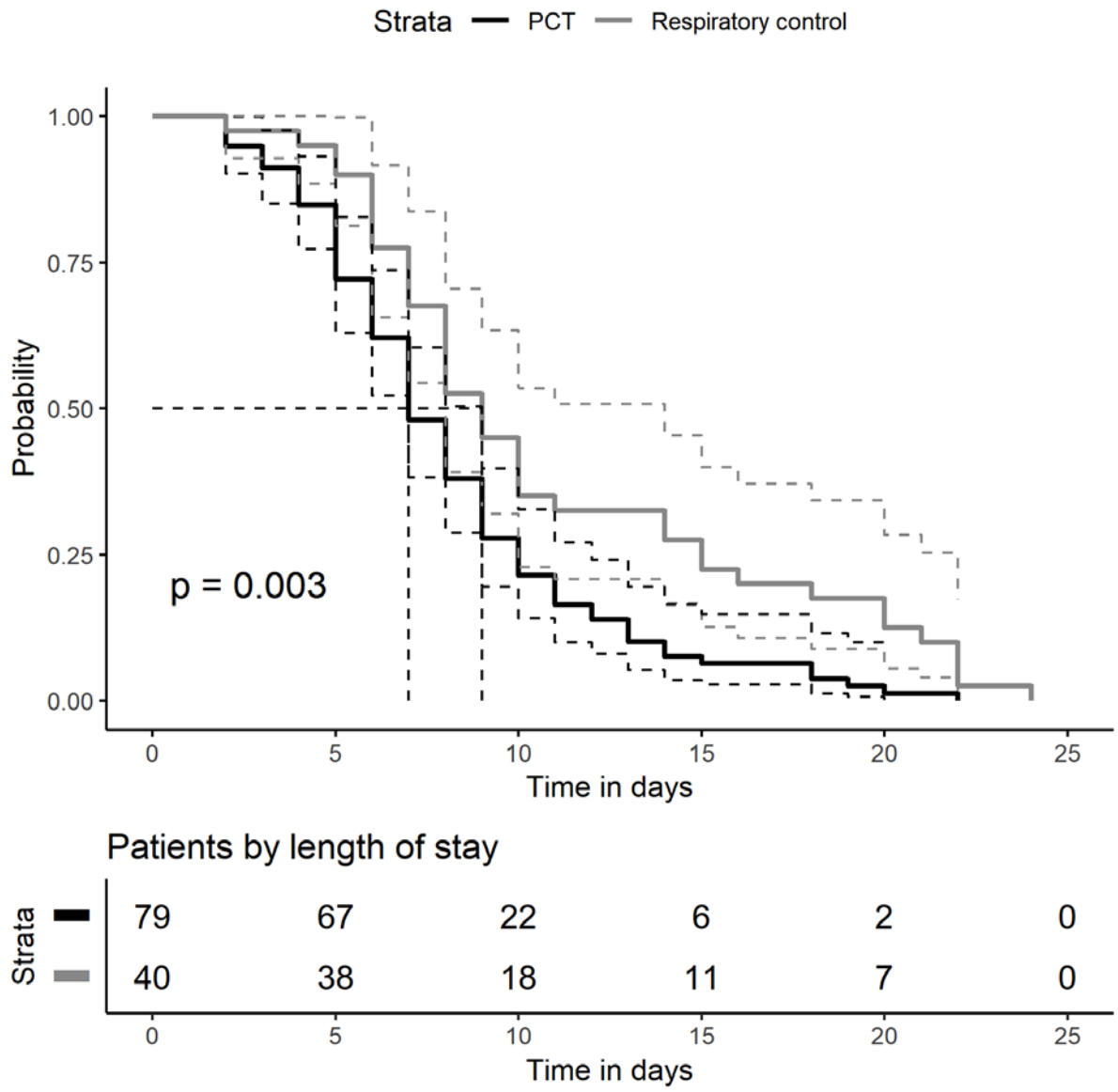


Figure 4. Comparison of time to discharge probability for PCT versus respiratory control arms- Kaplan–Meier curves. Median probability of discharge is given by the horizontal dashed line.

545 **Table 4. PCT algorithm compliance**

PCT level (μg/L)	Algorithm recommendation	Number of patients	Number of PCT test results	Number of patients compliant with algorithm	Number of patients non-compliant with algorithm	Percentage of patients compliant with algorithm
≤0.05 to <0.25	Antimicrobial therapy discouraged	67	119	7	60	10%
≥0.25	Antimicrobial therapy encouraged	25	44	25	0	100%

546